PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/40, 31/70, 31/19, C07H 5/06, C07D 207/16, C07C 51/41 // 59/84

A1

(11) International Publication Number: **WO 99/52528**

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/IB99/00626

(22) International Filing Date: 9 April 1999 (09.04.99)

(30) Priority Data:

843/98	11 April 1998 (11.04.98)	CH
618/99	31 March 1999 (31.03.99)	CH

(81) Designated States: CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(71) Applicant *(for all designated States except US)*: ERREKAPPA EUROTERAPICI S.P.A. [IT/IT]; Via Ciro Menotti, 1/A, I-20129 Milan (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: GIORGETTI, Paolo, Luca, Maria [IT/IT]; Via Ciro Menotti, 1/A, I-20129 Milan (IT).

(74) Agent: MASPOLI, René, A.; Patentanwaltsbureau R.A. Maspoli, Witikon-Zentrum, P.O. Box 191, CH-8053 Zürich (CH).

(54) Title: PHARMACEUTICAL PREPARATIONS CONTAINING HYDROSOLUBLE KETOPROFEN SALTS AND THEIR APPLICATION

(57) Abstract

The new pharmaceutical preparations contain hydrosoluble salts obtained through a reaction between Ketoprofen and Glucosamine and/or Proline and/or Hydroxyproline from 0.01 to 30 % of the mass. Such preparations are useful for anti-inflammatory and antalgic treatment of joints and mucous membranes.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL PREPARATIONS CONTAINING HYDROSOLUBLE KETOPROFEN SALTS AND THEIR APPLICATION

This invention refers to the use of soluble Ketoprofen salts with amino acids for administration through the injectable, transdermal/mucosal and oral routes.

These new compounds in addition to increasing the solubility of the active substance, are also able to increase the speed of absorption and the tolerability of the anti-inflammatory drug, as well as increasing the capacity to localize themselves in the inflammed sites in a preferential manner, particularly in inflammed joints and cartilaginous structures.

Ketoprofen is one of the most active non-steroidal anti-inflammatory drugs and, within its class of products (propionic acid derivatives), is the one with the most rapid anti-inflammatory and analgesic activity. Ketoprofen's anti-inflammatory action is exerted through various mechanisms:

a) inhibition of prostaglandin synthesis;
b) counteraction of pro-inflammatory peptide activity (e.g. bradykinin);
c) stabilization of cellular and liposomial membranes;
d) platelet anti-aggregating activity;

Ketoprofen is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, acute gout, osteoarthrosis in various locations, sciatic pain, radiculitis, myalgia, bursitis, tendonitis, tendosynovitis, synovitis, capsulitis, very severe bruises, sprains, dislocations, muscular dilaceration, phlebitis, superficial thrombophlebitis, lymphangitis, painful inflammatory dental, ENT, and urinary tract affections and in pneumology. Injectable Ketoprofen (i.m. and i.v.) is especially indicated for the symptomatic treatment of acute pain due to inflammation of the muscular-skeletal apparatus. Topical Ketoprofen

is indicated for the treatment of myalgia, muscular dilacerations, bruises, sprains, dislocations, muscular dilaceration, phlebitis, superficial thrombophlebitis, lymhangitis.

The pharmacological tests performed with Ketoprofen have demonstrated the substance's excellent tolerability and lack of acute and chronic toxicity following local application. In fact, dermal application of high quantities over extended intact and abraded surface areas in experimental animals did not induce any local or general harm, even after long term treatment. Ketoprofen, vehicled in suitable excipients and applied to the skin, is absorbed gradually. It has a half-life of 1.6 to 1.9 hours. Peak concentration following intramuscular administration is reached within 30 min.; peak mean value is 10.4 mcg/ml.

Ketoprofen's pharmacokinetic behaviour in synovial fluid is particularly interesting; and in view of the fact that this subject is the strategic part of this patent it, therefore, requires brief mention.

In medical practice it has been noted that there is a limited correlation between clinical response of patients treated with anti-inflammatories and the dose administered, as well as the consequent plasma levels. This phenomenon can be correlated with the fact that the plasma concentrations are not a suitable measure of drug concentration in the joints, which are the site of the inflammatory reaction.

It is, therefore, useful to evaluate the active substance concentration in synovial fluid after oral, transdermal or intramuscular administration of a NSAID. Netter et al. *(Netter P. et all., Clin. Pharmacol. Ther., 42: 555-561, 1987)* investigated Ketoprofen levels in plasma and synovial fluid in 37 patients (23 males and 14 females) by taking samples at various

intervals between 15 minutes and 15 hours after intramuscular administration of 100 mg.

The results obtained demonstrate that Ketoprofen penetrates promptly into the joints, in view of the significant concentrations that are detectable even 15 minutes after administration.

The maximum serum concentration is reached after 30 minutes (6.5 μg/ml); whilst equilibrium, i.e.: when serum and synovial concentrations are equivalent, is reached after 3.5 hours (1.3 μg/ml). After 8 to 15 hours from intramuscular administration of 100 mg Ketoprofen concentrations in synovial fluid are trebble those observable in serum. The AUC of the free Ketoprofen fraction in serum is 127 $hr*ng*ml^{-1}$, whilst in synovial fluid it is 119 $hr*ng*ml^{-1}$. Mean resident time in the joints was about three times longer than that observed in serum.

Ballerini et al. (*Ballerini R. et all., Int. J. Clin. Pharm. Res VI: 69-72, 1986)* also investigated the concentrations of Ketoprofen in the joints and in circulation. They administered a Ketoprofen gel to 6 patients who were to undergo a knee operation and in whom it was possible to determine the presence of the active substance in the intraarticular adipose tissue, in the capsular tissue and in synovial fluid. The gel was applied once a day for three days; the operations were performed 12 hours after the last administration.

Ketoprofen was detectable from the 2nd hour (6.3 ng/ml) and reached peak concentration after six hours (18.2 ng/l) with values that remained constant for 12 hours. In synovial fluid mean values after 12 hours were 1.31 mcg/g, whilst in intraarticular adipose tissue they were 4.70 mcg/g and in the capsular tissue 2.36 mcg/g. The data obtained show a greater active substance concentration in the joint than in systemic circulation

indicating a direct transdermal diffusion in the joint without direct involvement of circulatory flow, in which the active principle is present only due to local diffusion.

Kohler et al. *(Kohler G. et all., Sem. Hop. Par., 48: 3210-3213, 1983)* investigated 16 patients affected by rheumatoid polyarthritis or deforming arthrosis subjected to surgical procedures. The patients were treated with Ketoprofen 100 mg administered i.m. approximately 3 hours before the operation.

The mean values observed were 0.85 µg/g in synovial fluid, 0.32 µg/g in the synovial membrane, 0.25 µg/g in bone, 0.26 µg/g in muscle, 0.28 µg/g in fat, and 1.39 µg/g in blood.

Finally Kennedy *(Kennedy A.C. Sem. Hop. Par., 48: 3206-3209, 1983)* investigated Ketoprofen levels in the synovial fluid of patients affected by rheumatoid arthritis, by treating 6 subjects with 100 mg and 5 subjects with 50 mg, administered orally. The resulting concentrations demonstrated that in synovial fluid, after administration of Ketoprofen 50 mg, the peak (0.91 µg/ml) appears approximately two hours after the plasma peak; whilst with a 100 mg dose synovial concentrations remained practically stable for a period of 3 to 6 hours after treatment.

It is, therefore, possible to conclude that, following treatment through various routes of administration, the intraarticular Ketoprofen concentrations reach peak levels later with respect to those observable in serum and plasma, but remain at higher levels than the latter for a longer period after treatment and always with higher values compared to those present in circulatory flow.

Ketoprofen is mainly excreted with urine (>50% in the form of metabolites) and only a minimal percentage is eliminated with the feces (1%).

Toxicity studies have demonstrated Ketoprofen's low toxicity and high therapeutical ratio. The oral LD_{50} in the rat is 165 mg/kg; whilst in the mouse, for various routes of administration, it is between 365 and 662 mg/kg.

Ketoprofen, 3-Benzoyl-α-methylbenzeneacetic acid, $C_{16}H_{14}O_3$; mol wt 254,29 is practically insoluble in water, in acid solutions, and soluble in alkaline solutions. This substance's solubility in water can be modified when the molecule is salified with inorganic or organic bases.

The use of Ketoprofen salts has always attracted substantial interest because of the evident improvements obtainable with regard to bioavailability, tolerability and compliance (use of more suitable and specific pharmaceutical presentations).

Numerous developments and patents have been obtained in this field; for example it is possible to mention the use of K sodium salt, Arginine, Lysine and Methylglucamine salt for use in soft gelatin capsules(PCT/FR91/00273).

Another patent (PCT/US94/09581) describes the composition of anti-inflammatories such as Ibuprofen, Naproxen, Ketoprofen, among which Lysine, Choline Arginine, Glucosamine salts.

Particular interest is directed towards the following three amino acids which, thanks to their basicity, solubility and pharmacological properties, can form interesting Ketoprofen salts: Glucosamine, Proline and Hydroxyproline.

Glucosamine, 2-Amino-2-deoxy-D-glucose, $C_6H_{13}NO_5$, mol wt 179.17, an amino sugar that occurs naturally in the

human body, is used for the biosynthesis of hyaluronic acid in synovial fluid and proteoglycans of the interstitial substance of joint cartilage.

Glucosamine is normally synthesized starting from glucose. During arthrosis there is a metabolic deficit in the biosynthesis of Glucosamines and proteoglycans. In this condition exogenous supply of Glucosamine compensates the substance's endogenous deficit, it stimulates biosynthesis of proteoglycans, exerts a trophic action on articular cartilage and favours fixation of sulphur for the synthesis of chondroitinsulfuric acid. All these activites have a favourable effect on cartilage degenerative processes that are at the basis of arthrosis.

Proline (l-Proline, $C_5H_9N_2$, mol wt 115.13) and Hydroxyproline (trans-4-Hydroxyproline, $C_5H_9NO_3$, mol wt 131.13) are two special amino acids since they do not possess an aminic group ($-NH_2$), but an iminic group (-NH-). Their presence in special polypeptide chain sites allows proteins certain curves which have structural importance. Hydroxyproline is not present in the majority of proteins and is typical of connectival proteins (collagen, elastin); it is contained in collagen as an essential component at a ratio of 10%.

Ketoprofen Glucosamine, Proline and Hydroxyproline salts have been investigated following injectable, topical and oral administration for the assessment of their anti-inflammatory activity.

There are two methods of preparation for Ketoprofen Glucosamine, Proline and Hydroxyproline salts

a) extemporaneous preparation in aqueous solvent

b) preparation using organic solvent

The first method appears to be the most logical when one wishes to obtain a salt; in such case, the solution can be used promptly for the preparation of water based

formulations (injectable preparations, water emulsions, oral solutions, etc.).

The second method is used for the preparation of the salt in order to achieve a solid substance for use in solid preparations such as, for example, tablets, granules, suppositories, etc.

Preparation of Ketoprofen Glucosamine salt through the aqueous route is carried out with stoichiometric quantities at the ratio of 1:1 of Ketoprofen and Glucosamine base, according to the following procedure:

1# Weigh 179.17 g of Glucosamine base and dissolve in 300 ml of purified water.

2# After complete dissolution, add and dissolve under stirring 254.29 g of Ketoprofen acid.

3# To aid dissolution, thermostat to 35-40°C, control the pH which must be neutralized by adjustment, if required, adding either Ketoprofen (if the pH is basic) or Glucosamine base (if the pH is acid).

4# Cool to room temperature and bring to 1 litre volume with water.

5# Filter through a sterilizing membrane with 0.22 micron porosity. A Ketoprofen Glucosamine salt solution has thus been obtained having a concentration of 433.4 g/litre.

Preparation of Ketoprofen Proline salt through the aqueous route is carried out with stoichiometric quantities at the ratio of 1:1 of Ketoprofen and Proline base, according to the following procedure:

1# Weigh 115.13 g of Proline base and dissolve in 300 ml of purified water.

2# After complete dissolution, add an dissolve under stirring 254.29 g of Ketoprofen acid.

3# To aid dissolution, thermostat to 35-40°C, control the pH which must be neutralized by adjustment, if required, adding either Ketoprofen (if the pH is basic) or Proline base (if the pH is acid).

4# Cool to room temperature and bring to 1 litre volume with water.

5# Filter through a sterilizing membrane with 0.22 micron porosity. A Ketoprofen Proline salt solution has thus been obtained having a concentration of 369.42 g/litre.

Preparation of Ketoprofen Hydroxyproline base through the aqueous route is carried out with stoichiometric quantities at the ratio of 1:1 of Ketoprofen and Hydroxyproline base, according to the following procedure:

1# Weigh 131.13 g of Hydroxyproline base and dissolve in 300 ml of purified water.

2# After complete dissolution, add an dissolve under stirring 254.29 g Ketoprofen acid.

3# To aid dissolution, thermostat to 35-40°C, control the pH which must be neutralized by adjustment, if required, adding either Ketoprofen (if the pH is basic) or Hydroxyproline base (if the pH is acid).

4# Cool to room temperature and bring to 1 litre volume with water.

5# Filter through a sterilizing membrane with 0.22 micron porosity. A Ketoprofen Hydroxyproline salt solution has thus been obtained having a concentration of 385.42 g/litre.

Preparation with organic solvent involves dissolution of Ketoprofen in organic solvent (for example pure ethanol) and salification by adding and dissolving Glucosamine, or Proline, or Hydroxyproline, according to the above mentioned stoichiometric ratios.

This is followed by filtration through a porous sintered glass septum, then elimination of the organic solvent using a rotating vacuum evaporator. The residue obtained is dried in a vacuum oven, then reduced and dimensioned to powder.

The three above mentioned Ketoprofen salts were compared with Ketoprofen acid and Ketoprofen sodium salt in animal studies.

Investigation in experimental animals evidenced a surprising increase in anti-inflammatory and antalgic activity.

In particular:

a) Injection of Ketoprofen Glucosamine salts produced a high active substance concentration in the inflammed site, which was much greater than that observed with Ketoprofen sodium salt. The Proline and Hydroxyproline salts reach intermediate concentrations between the sodium salt and the Glucosamine salt.

b) Ketoprofen Glucosamine, Proline and Hydroxyproline salts administered orally indicated kinetic parameters that were significantly different with respect to Ketoprofen acid and Ketoprofen sodium salt.

c) In the above mentioned tests, Ketoprofen Glucosamine salt shows a surprising affinity for cartilage and connective tissue enabling targetted vehicolation to the inflammatory sites.

The pharmacological and pharmacodynamic properties of Ketoprofen Glucosamine, Proline and Hydroxyproline salts enable the preparation of formulations for rational pharmaceutical presentantions that lead to an improvement in drug activity, thus increasing compliance.

This invention is characterized by the claims that follow and may be described in a more detailed manner with the aid of formulation examples that are not to be considered as a limit for the invention.

Furthermore, the anti-inflammatory activity of Ketoprofen Glucosamine salt and Ketoprofen Lysine salt, compared to that of Ketoprofen, has been assessed in the rat using the carrageen edema model and the foreign body (sponge) method.

The carrageen edema tests in the rat were carried out on 80 male animals of the Wistar (Charles River, Calco, LC, Italy) strain weighing 160±5 g.

The Winter et al. method was used which enables assessment of drug activity in the acute phase of the inflammatory process that is essentially related to increased vascular (edema) permeability and substantial infiltration of polymorphonucleated granulocytes in the exudate.

In particular, 100 µl of carrageen at a 1% concentration dissolved in sterile physiological solution, were injected into the hind paw aponeurosis of animals that had been fasted (water ad libitum) from the evening prior to the experiment.

In order to obtain greater uniformity in the development of the edema, the animals were treated orally with 5 ml of physiological solution 2 hours before the test.

Evolution of edema induced by administration of carrageen was assessed with the plethysmographic method using a device (plethysmometer, mod. 7150) manufactured by U. Basile, Comerio, Varese, Italy.

Measurement of paw volume was carried out immediately after injection of the phlogogenic agent (T0) and at each hour up to the 6th hour following treatment. The animals, randomly divided into 8 experimental groups (10 per group), were treated orally (using a gastric probe) with Ketoprofen Glucosamine salt, Ketoprofen Lysine salt and with Ketoprofen, 30 minutes before carrageen, according to the following experimental protocol:

Controls (physiologial solution, 1 ml/kg)	10 animals
Ketoprofen Glucosamine salt (0.5 mg/kg)	10 animals
Ketoprofen Glucosamine salt (1 mg/kg)	10 animals
Ketoprofen Glucosamine salt (2 mg/kg)	10 animals

Ketoprofen Lysine salt (0.5 mg/kg)	10 animals
Ketoprofen Lysine salt (1 mg/kg)	10 animals
Ketoprofen Lysine salt (2 mg/kg)	10 animals
Ketoprofen (10 mg/kg)	10 animals

Since Ketoprofen's anti-inflammatory activity, as that of all propionic acid derivatives, is largely due to inhibition of the cyclooxygenase enzyme and, therefore, blockade of arachidonic acid oxidative cascade, the experimental "sponge" model in the rat described by Higgs et al. is particularly suitable for the evaluation of the vascular exudation phenomenon and related new formation of primary prostaglandin.

These tests involved the use of 100 male CD strain rats (Charles River, Calco, LC, Italy) weighing 180±8 g. The animals were fasted for 12 hours (water ad libitum) before being used for the experiment.

The inflammatory reaction with the formation of exudate was induced by using sterilized polyester sponges (4 x 1.5 x 0.5 cm) soaked in carrageen dissolved at a 2% concentration in sterile physiological solution. The rats were anesthetized lightly with ether and two sponges per rat were implanted subcutaneously in a previously shaven dorsal area. The animals, randomly divided into 10 experimental groups (10 per group), were treated orally (using a gastric probe) with Ketoprofen Glucosamine salt, Ketoprofen Lysine salt and Ketoprofen, immediately after implantation of the sponges (T0) according to the following experimental protocol:

Controls (physiologial solution, 1 ml/kg)	10 animals
Ketoprofen Glucosamine salt (0.5 mg/kg)	10 animals
Ketoprofen Glucosamine salt (1 mg/kg)	10 animals
Ketoprofen Glucosamine salt (2 mg/kg)	10 animals
Ketoprofen Glucosamine salt (4 mg/kg)	10 animals
Ketoprofen Lysine salt (0.5 mg/kg)	10 animals

Ketoprofen Lysine salt (1 mg/kg)	10 animals
Ketoprofen Lysine salt (2 mg/kg)	10 animals
Ketoprofen Lysine salt (4 mg/kg)	10 animals
Ketoprofen (10 mg/kg)	10 animals

The sponges were removed 8 hours later after having sacrificed the animals by ether euthanasia, and immediately placed in large polyethylene 50 ml test tubes containing 10 ml of heparinized physiological solution. The test tubes were then subjected to centrifugation (1000 rotations; 15 minutes), followed by removal of the sponges and accurate measurement of the volume of the remaining fluid. Always using the Higgs et al. method, the acid lipids present in the fluid were extracted in chloroform with prior dilution in ethanol and acidification to pH 3. After complete evaporation of the chloroform, the remaining dry residue was dissolved in physiological solution and used for the immunoenzymatic assay of prostaglandin E_2 (PGE_2).

The following substances and experimental materials were used for these tests: Ketoprofen Glucosamine salt and ketoprofen Lysine salt, Ketoprofen and type IV carrageen (Sigma-Aldrich, Milan, Italy); a kit for the immunoenzymatic assay of PGE_2 (Amersham, Milan, Italy). All the other reagents used for the tests were purchased from Merck-Bracco (Milan, Italy).

The data obtained during these tests were processed with the variance analysis (ANOVA) and Student's "t" test for independent data, considering significant the differences with $p<0.05$. Multiple comparisons between the various experimental groups were carried out using the statistical Tukey-Kramer test. The area underneath the curve (AUC) was calculated with the trapezoid method using a computer programme (Microcal Origin, version 3.5).

The results obtained for the carrageen edema test in the rat indicate that Ketoprofen Glucosamine salt, administered orally at doses of 0.5, 1 and 2 mg/kg, possesses anti-inflammatory activity. The anti-edematogenic effect of the test compound is dose-dependent. In fact, considering the values obtained by measuring the area underneath the curve (AUC), Ketoprofen Glucosamine salt significantly inhibits ($p<0.001$) the reaction process by 30%, 48% and 72% at the oral doses of 0.5, 1 and 2 mg/kg respectively (Tables 1-2).

The anti-inflammatory activity observed with Ketoprofen Glucosamine salt is comparable with that obtained by administering Ketoprofen Lysine salt to rats at the oral doses of 0.5, 1 and 2 mg/kg. In fact, the ED_{50} values of the two compounds (extrapolated from the data obtained with the AUC) resulted equal to 1.104 mg/kg per os (95% confidence limit: 0.733-1.474) and 1.383 mg/kg per os (95% confidence limit: 1.198-1.567) respectively for Ketoprofen Glucosamine salt and Ketoprofen Lysine salt (Table 2).

In this test Ketoprofen (used as internal positive standard) also resulted as having anti-inflammatory activity. In fact, this substance administered to rats at the dose of 10 mg/kg per os, inhibits (54.1%; $p<0.001$) the inflammatory reaction caused by injection of carrageen in the paw aponeurosis (Tables 1-2).

The results obtained in the test with induction of edema using foreign body implantation (sponge) in the rat and reported in Table 3, clearly indicate that Ketoprofen Glucosamine salt controls the vasculo-exudative inflammatory response in a dose dependent manner (0.5, 1, 2 and 4 mg/kg per os). In fact, Ketoprofen Glucosamine salt is able to significantly counteract the evolution of the reaction above all in

terms of minor formation of inflammatory exudate correlated with singificant inhibition of PGE2 activity in such exudates (Table 3).

Ketoprofen Lysine salt administered to animals at a dose of 0.5, 1, 2 and 4 mg/kg per os, also demonstrated that it is able to control the inflammatory response of the host of the subcutaneous foreign body implant (Table 3).

Table 1 illustrates the anti-inflammatory activity of Ketoprofen Glucosamine salt (KGS), Ketoprofen Lysine salt (KLS) and Ketoprofen (KETO) in the rat: carrageen edema test. The data represent the mean ± MSE of 10 rats per group. The compounds were administered orally 60 min before the inflammatory agent (carrageen 1%). Baseline paw volume was 1.70±0.02 ml (n=80).

Table 1

COMPOUND	EVOLUTION OF PAW VOLUME (delta in ml) at:					
mg/kg/os	1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour
CONTROLS	0.40±0.02	0.71±0.02	0.87±0.03	0.93±0.03	0.90±0.04	0.84±0.04
KGS 0.5	0.28±0.02	0.51±0.03	0.62±0.04	0.65±0.04	0.62±0.05	0.56±0.05
KGS 1	0.23±0.01	0.39±0.02	0.46±0.02	0.48±0.02	0.45±0.02	0.39±0.03
KGS 2	0.11±0.02	0.20±0.02	0.26±0.03	0.28±0.03	0.25±0.03	0.16±0.02
KLS 0.5	0.32±0.02	0.53±0.03	0.66±0.04	0.70±0.03	0.68±0.02	0.64±0.03
KLS 1	0.24±0.02	0.43±0.03	0.54±0.03	0.59±0.03	0.57±0.03	0.49±0.03
KLS 2	0.13±0.02	0.23±0.02	0.28±0.02	0.29±0.02	0.28±0.02	0.23±0.03
KETO 10	0.19±0.02	0.33±0.03	0.41±0.02	0.42±0.02	0.40±0.03	0.37±0.03

Table 2 illustrates the areas underneath the curve (AUC) related to evolution through time of the increases in paw volume.

The compounds were administered orally 60 min before carrageen. The AUC were calculated with the trapezoid method [in ordinates: paw volume (delta in ml); in abscissa: time (from 0 to 6 hours)]. All the differences versus controls were highly significant ($p<0.001$) (ANOVA+ Tukey-Kramer test).

Table 2

SUBSTANCE	ORAL DOSE mg/kg	No. rats	AUC (mean ± MSE)	% inhibition vs controls	ORAL ED_{50} mg/kg (95% conf. Lim.)
CONTROLS	-	10	4.23±0.26	-	-
KGS	0.5	10	2.96±0.15	30.0	1.104
KGS	1	10	2.20±0.13	48.0	(0.733-1.474)
KGS	2	10	1.18±0.06	72.1	
KLS	0.5	10	3.21±0.17	24.1	1.383
KLS	1	10	2.62±0.12	38.0	(1.198-1.567)
KLS	2	10	1.33±0.07	68.6	
KETO	10	10	1.94±0.10	54.1	-

Table 3 indicates the effect of Ketoprofen Glucosamine salt (KGS), Ketoprofen Lysine salt (KLS) and Ketoprofen (KETO) on the concentration of prostaglandin E_2 (PGE_2) present in the inflammatory exudate (IE) obtained 8 hours after subcutaneous implantation of two polyester sponges soaked in carrageen (0.5%) in rats. The compounds were administered orally immediately after implantation of the sponges. The values are expressed as mean±MSE. The % inhibition versus controls is placed in brackets.

a: $p<0.05$ b: $p<0.01$; c: $p<0.001$ (ANOVA + Tukey-Kramer test).

Table 3

SUBSTANCE	DOSE mg/kg os	No. rats	IE (ml)	PGE_2 (ng/ml)
CONTROLS	-	10	5.15±0.28 (----)	98.7±4.7 (----)
KGS	0.5	10	3.87±0.27 (24.8)b	67.6±4.1 (31.5)c
KGS	1	10	3.56±0.28 (30.9)c	60.5±3.0 (38.7)c
KGS	2	10	2.53±0.22 (50.9)c	49.9±2.1 (49.4)c
KGS	4	10	1.05±0.09 (79.6)c	24.9±2.3 (74.8)c
KLS	0.5	10	4.33±0.26 (15.9)a	78.1±3.7 (20.9)b
KLS	1	10	3.82±0.15 (25.8)b	67.9±3.5 (31.2)c
KLS	2	10	2.97±0.19 (42.3)c	55.6±2.3 (43.7)c
KLS	4	10	1.68±0.14 (67.4)c	32.8±1.8 (66.8)c
KETO	10	10	2.13±0.15 (58.6)c	49.6±3.0 (49.7)c

Table 4 contains the values of the ED_{50} for Ketoprofen Glucosamine salt (KGS), Ketoprofen Lysine salt (KLS) on the concentration of prostaglandin E_2 (PGE_2) present in the inflammatory exudate (IE) obtained 8 hours after implantation of two polyester sponges soaked in carrageen (0.5%) in rats. The compounds were administered orally immediately after implantation of the sponges. The values of the Efficacy Dose (ED_{50}) were calculated using the data reported in table 3. The values in brackets represent the 95% confidence limits.

Table 4

SUBSTANCE	DOSE mg/kg os	IE (ml) (ORAL ED_{50} mg/kg)	PGE, (ORAL ED_{50} mg/kg)
KGS	0.5		
KGS	1	2.092	1.989
KGS	2	(1.802-2.381)	(1.848-2.131)
KGS	4		
KLS	0.5		
KLS	1	2.714	2.610
KLS	2	(2.334-3.094)	(2.215-3.005)
KLS	4		

The invention is characterized by the nine claims that follow.

The following represent examples of pharmaceutical preparations in accordance with the invention.

EXAMPLE NO. 1: INJECTABLE PREPARATION FOR INTRAMUSCULAR ADMINISTRATION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Benzyl alcohol	90 mg
Sodium chloride	27 mg
Water for injectable preparations	up to: 3 ml

EXAMPLE NO. 2: INJECTABLE PREPARATION FOR INTRAVENOUS ADMINISTRATION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Fructose	700 mg
Water for injectable preparations	up to: 10 ml

EXAMPLE NO. 3: LARGE VOLUME PREPARATION FOR INTRAVENOUS ADMINISTRATION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Anhydrous glucose	25 g
Water for injectable preparations	up to: 500 ml

EXAMPLE NO. 4: TABLETS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	

Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Corn starch	100 mg
Pyrogenic silica	15 mg
Microcrystalline cellulose	110 mg
Talc	3 mg
Magnesium stearate	2 mg

EXAMPLE NO. 5: GASTRORESISTANT TABLETS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Nucleus excipients:	
Granular cellulose	110 mg
Dried spray lactose	100 mg
Talc	5 mg
Glycerol beenate	15 mg
Coating excipients:	
Cellulose acetophthalate	10 mg
Diethylphthalate	1 mg
Titanium dioxide	2 mg
Talc	8 mg

EXAMPLE NO. 6: COATED TABLETS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Nucleus excipients:	
Granular cellulose	110 mg
Magnesium oxide	100 mg
Talc	5 mg
Glycerol beenate	15 mg
Coating excipients:	
Methylcellulose	10 mg

Triacetin	1 mg
Titanium Dioxide	1 mg
E172	1 mg
Talc	2 mg

EXAMPLE NO. 7: CAPSULES

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Pyrogenic silica	5 mg
Levilite	20 mg
Cellulose	50 mg
Talc	2 mg
Magnesium stearate	3 mg
White non-transparent size 1 capsules	

EXAMPLE NO. 8: GASTRORESISTANT CAPSULES

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Pyrogenic silica	5 mg
Levilite	20 mg
Cellulose	50 mg
Talc	2 mg
Magnesium stearate	3 mg
White non-transparent size 1 capsules	
Coating excipients:	
Methylcellulose	10 mg
Triacetin	1 mg
Titanium Dioxide	2 mg
E172	2 mg

Talc	5 mg

EXAMPLE NO. 9: SOFT CAPSULES

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Mineral oil	115 mg
Food gelatin	50 mg
Titanium dioxide	5 mg

EXAMPLE NO. 10: EXTEMPORANEOUS GRANULES

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Mannitol	315 mg
Maltodextrin based lyophilized orange flavouring	3500 mg
Lemon flavouring	80 mg
Potassium acesulfame	20 mg

EXAMPLE NO. 11: SLOW RELEASE TABLETS (MATRIX SYSTEM)

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Methylcellulose	50 mg
Ethylcellulose	100 mg
Talc	20 mg
Magnesium stearate	5 mg

EXAMPLE NO. 12: CAPSULES WITH TARGETTED RELEASE

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	85 mg

equivalent to Ketoprofen acid	50 mg
Excipients:	
Pyrogenic silica	5 mg
Levilite	20 mg
Cellulose	50 mg
Talc	2 mg
Magnesium stearate	3 mg
White non-transparent size 1 capsules	
Coating excipients:	
Eudragit S	20 mg
Eudragit L	20 mg
Triacetin	1 mg
Titanium dioxide	2 mg
E172	2 mg
Talc	5 mg

EXAMPLE NO. 13: SLOW RELEASE GRANULES

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Eudragit S	30 mg
Eudragit L	30 mg
Lactose	2000 mg
Saccharin sodium	20 mg
Wild fruits flavouring	50 mg

EXAMPLE NO. 14: SLOW RELEASE ORAL SUSPENSIONS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	1.7 g
equivalent to Ketoprofen acid	1 g
Excipients:	
Eudragit S	3 g
Eudragit L	3 g

Sucrose	20 g
Arabic gum	0.5 g
Saccharin sodium	0.2 g
Wild fruits flavouring	0.2 g
Sodium benzoate	0.1 g
Purified water	up to: 100 ml

EXAMPLE NO. 15: CHEWING GUM

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Gum	2.0 g
Sucrose	2.0 g
Orange flavouring	0.1 g
Lemon flavouring	0.1 g
Talc	0.01 g

EXAMPLE NO. 16: GINGIVAL GEL

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	3.4 g
equivalent to Ketoprofen acid	2 g
Excipients:	
Carbopol 940	1.0 g
Sodium hyaluronate	1.0 g
Methyl-p-hydroxybenzoate	0.1 g
Purified water	up to: 100 g

EXAMPLE NO. 17: MOUTHWASH SOLUTION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	1.7 g
equivalent to Ketoprofen acid	1 g
Excipients:	
Ethyl alcohol 95°	10.0 g
Sorbitol 70%	30.0 g

Saccharin sodium	0.1 g
Pluronic	0.9 g
Mint flavouring	0.1 g
Potassium sorbate	0.5 g
Purified water	up to: 100 ml

EXAMPLE NO. 18: SOLUTIONS FOR CANALAR TREATMENT

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 g
Excipients:	
Chlorhexidine gluconate	0.5 g
Purified water	up to: 100 ml

EXAMPLE NO. 19: SUPPOSITORIES

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	170 mg
equivalent to Ketoprofen acid	100 mg
Excipients:	
Witepsl H 15	up to: 4 g

EXAMPLE NO. 20: VAGINAL BOUGIES

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Supposire BS2X	up to: 3.5 g

EXAMPLE NO. 21: SOLUTIONS FOR VAGINAL IRRIGATION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	85 mg
equivalent to Ketoprofen acid	50 mg
Excipients:	
Tween 20	500 mg
Rose perfume	100 mg

Propylene glycol	1000 mg
Methyl-p-hydroxybenzoate	0.100 mg
Propyl-p-hydroxybenzoate	0.050 mg
Purified water	up to: 100 ml

EXAMPLE NO. 22: VAGINAL CREAM WITH APPLICATOR

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Mineral oil	10 g
Tefose 63	18 g
Propylene glycol	3 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Purified water	up to: 100 g

EXAMPLE NO. 23: VAGINAL GEL WITH APPLICATOR

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Carbopol 934	2 g
Propylene glycol	20 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Purified water	up to: 100 g

EXAMPLE NO. 24: VAGINAL FOAM

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Sodium Lauryl sulfate	1 g
PVP	2 g

Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Benzyl alcohol	0.5 g
Purified water	up to: 100 g

Packed in a pressurized can with an applicator, dosed at a ratio of 45 g of foam with 5 g of isobutane

EXAMPLE NO. 25: SOLUTIONS FOR EAR APPLICATION

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Propylene glycol	up to: 100 g

EXAMPLE NO. 26: EYEDROP SOLUTIONS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	1.7 g
equivalent to Ketoprofen acid	1 %
Excipients:	
Sodium chloride	0.9 g
Benzalconium chloride	0.1 g
Sterile Purified water	up to: 100 ml

EXAMPLE NO. 27: CREAM

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Nesatol	8 g
Xalifin 15	15 g
Propylene glycol	3 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g

Purified water	up to: 100 g

EXAMPLE NO. 28: GEL

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Natrosol 250 HH	2 g
Propylene glycol	10 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Purified water	up to: 100 g

EXAMPLE NO. 29: OINTMENT

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Amerchol CAB	8 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Vaseline	up to: 100 g

EXAMPLE NO. 30: LOTION

SUBSTANCE	QUANTITY FOR 1 UNIT
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Ethyl alcohol 95°	10 g
Glycerin	10 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Purified water	up to: 100 ml

EXAMPLE NO. 31: SOLUTION

SUBSTANCE	QUANTITY FOR 1 UNIT

Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Purified water	up to: 100 ml

EXAMPLE NO. 32: TOPICAL FOAM WITH PROPELLENTS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Tween 20	3 g
PVP k 30	3 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Benzyl alcohol	0.5 g
Lavender perfume	0.2 g
Purified water	up to: 100 g

Packed in a pressurized can with an applicator, dosed at a ratio of 45 g of foam with 5 g of isobutane

EXAMPLE NO. 33: FOAM WITHOUT PROPELLENTS

SUBSTANCE	**QUANTITY FOR 1 UNIT**
Active substance:	
Ketoprofen Glucosamine salt	17 g
equivalent to Ketoprofen acid	10 %
Excipients:	
Sodium Lauryl sulfate	1 g
PVP	2 g
Methyl-p-hydroxybenzoate	0.1 g
Propyl-p-hydroxybenzoate	0.05 g
Benzyl alcohol	0.5 g
Purified water	up to: 100 g

Packed in a can with an applicator

CLAIMS

1. Pharmaceutical preparations containing hydrosoluble Ketoprofen salts obtained by means of a reaction between Ketoprofen and Glucosamine and/or Proline and/or Hydroxyproline.
2. Pharmaceutical preparations in accordance with claim 1, containing 0.01 to 30% of the mass of Ketoprofen hydrosoluble salts.
3. Use of the pharmaceutical preparations in accordance with claim 1 for anti-inflammatory and antalgic treatment, especially those involving the joints, through oral, transdermal or intramuscular administration of such preparations.
4. Use in accordance with claim 3 in the form of injectable presentations, tablets, capsules, granules or suspensions.
5. Use of the pharmaceutical preparations in accordance with claim 1 for anti-inflammatory and antalgic treatment especially of the mucous membranes by injectable or topical administration of such preparations.
6. Use in accordance with claim 5 in the form of solution, irrigation solutions, mouthwash solutions, suppositories, vaginal bougies, gels, creams or foams.
7. Hydrosoluble salts contained in the preparations in accordance with claim 1, characterized by the fact that they are obtained from Ketoprofen and amino acids, in 0.8 to 1.2 times the equimolar quantities.
8. Hydrosoluble salts in accordance with claim 7, obtained in water solution form, characterized by the fact that synthesis is carried out at neutral pH at temperatures between 5° and 60°C and that the concentration of the salts obtained is $\geq 300\ g \cdot l^{-1}$.

9. Hydrosoluble salts in accordance with claim 7, obtained in solid form, characterized by the fact that synthesis is carried out in at least one suitable organic solvent which, after reaction, is eliminated at a high temperature and/or reduced pressure.

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/IB 99/00626

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 A61K31/70 A61K31/19 C07H5/06 C07D207/16
C07C51/41 //C07C59/84

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D C07C C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 07079 A (THE PROCTER & GAMBLE COMPANY) 16 March 1995 (1995-03-16) abstract page 2, line 28 - line 32 see page 3 lines 19,33,38 page 5, line 5 - line 11 ---	1-4
A	WO 96 16016 A (LABORATORIOS MENARINI) 30 May 1996 (1996-05-30) the whole document ---	1-9
A	US 4 748 174 A (VERONESI) 31 May 1988 (1988-05-31) abstract column 1, line 24 - line 40 column 3, line 1 - line 7 column 5 claims 1,11,28-34 ---	1-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1999	06/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO___9952528A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/00626

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 12451 A (HOECHST CELANESE CORPORATION) 9 June 1994 (1994-06-09) the whole document	7-9
A	PATENT ABSTRACTS OF JAPAN vol. 0, no. 0 & JP 63 093718 A (GREEN CROSS CORPORATION), 25 April 1988 (1988-04-25) abstract	7,8

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/IB 99/00626

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507079 A	16-03-1995	AU 7604194 A	27-03-1995
		BR 9407415 A	12-11-1996
		CA 2170485 A	16-03-1995
		EP 0717624 A	26-06-1996
		JP 9502202 T	04-03-1997
WO 9616016 A	30-05-1996	ES 2109858 A	16-01-1998
		AU 3983595 A	17-06-1996
US 4748174 A	31-05-1988	IT 1207994 B	01-06-1989
		DE 3700172 A	09-07-1987
		JP 2568401 B	08-01-1997
		JP 62252749 A	04-11-1987
WO 9412451 A	09-06-1994	US 5380867 A	10-01-1995
		US 5332834 A	26-07-1994
		AU 5730294 A	22-06-1994
		EP 0672029 A	20-09-1995
		JP 8503949 T	30-04-1996
		US 5399707 A	21-03-1995
JP 63093718 A	25-04-1988	NONE	